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A. DiLullo A. DiLullo
Name (Print) Signature

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Customer No.: 07278
PATENT TRADEMARK OFFICE

Docket No: 2094/1E285US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Kevin M. GORMAN, David R. PATTERSON, Jeffrey M. LINNEN and Keming SONG

Serial No.: 09/494,332 Art Unit: 1655

Filed: January 28, 2000 Examiner: J. GOLDBERG

For: OLIGONUCLEOTIDE PRIMERS FOR EFFICIENT MULTIPLEX DETECTION OF HEPATITIS C VIRUS (HCV) AND HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND METHODS OF USE THEREOF

DECLARATION OF KEVIN M. GORMAN UNDER 37 C.F.R. § 1.132

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

I, Kevin M. GORMAN, hereby declare and state as follows:

1. I am a citizen of the United States of America and am more than 21 years of age.

2. I presently hold the position of Research Scientist at Wyeth-Lederle Vaccines where I have been employed since September, 1999. Prior to this position, I held the position Research Scientist at Ortho-Clinical Diagnostics, Inc. (a subsidiary of Johnson & Johnson Co.). My qualifications are set forth more fully on the copy of my *Curriculum Vitae* attached hereto at Exhibit Tab 1.

3. I am one of the named inventors in the above-identified patent application. I make the following averments for myself and on behalf of my co-inventors.

4. I have read and am familiar with the instant application as it was filed in the U.S. Patent and Trademark Office (the "USPTO"). I have been advised by counsel, and therefore believe, that this application is based on and benefits from the earlier filing date of the prior provisional patent application serial no. 60/118,498 filed on February 3, 1999.

5. I have also read and am familiar with the pending claims of the application as amended August 27, 2001. I have been advised by counsel, and therefore believe, that among the pending claims in this application are ones directed to a polymerase chain reaction ("PCR") assay that is capable of

simultaneously detecting nucleic acids from both human immunodeficiency virus ("HIV") and hepatitis C virus ("HCV") in a sample.

6. I have also been advised by counsel, and therefore believe, that these claims have been rejected by the USPTO as being obvious over combinations of the following references:

(a) Han *et al.*, "Characterization of the Terminal Regions of Hepatitis C Viral RNA: Identiification of Conserved Sequences in the 5' Untranslated Region and Poly(A) Tails at the 3' End", *Proc. Natl. Acad. Sci. U.S.A.* 1991, 88:1711-1715 ("Han");

(b) U.S. Patent No. 6,001,558 issued December 14, 1999 to Backus *et al.* ("Backus");

(c) U.S. Patent No. 5,846,704 issued December 8, 1998 to Maertens *et al.* ("Maertens");

(d) Nedjar *et al.*, "Co-Amplification of Specific Sequences of HCV and HIV-1 Genomes by Using the Polymerase Chain Reaction Assay: A Potential Tool for the Simultaneous Detection of HCV and HIV-1", *J. of Virological Methods* 1991, 35:297-304 ("Nedjar"); and

(e) Ahern, "Biochemical Reagent Kits Offer Scientists Good Return on Investment", *The Scientist* 1995, 9(15):20 ("Ahern").

I have read and am familiar with each of these references.

7. Described herein are certain experiments relating to the PCR kits and assays that are recited in the pending claims of this application. These experiments were carried out by my co-inventors and myself, or by others working under our supervision and control. The results from those experiments demonstrate that, at the very best, persons similarly skilled in the art of molecular biology could have only been motivated to *try* using a combination of HIV and HCV-specific primers to design a viable PCR assay. In particular, and as demonstrated in the experiments described here, when this application was first filed (*i.e.*, as of the February 3, 1999 priority date) it was not possible to predict *a priori* whether a particular combination of primers would work in such an assay.

8. Specifically, the experiments described here relate to multiplex PCR assays that use primers designed to specifically amplify two separate regions of the HCV genome: the 5' non-coding (NC) region and the 3' NC region. At the time these experiments were performed, both the 5' NC and the 3' NC regions had been described and were known. For example, the 5' NC region is described in the Han reference cited in ¶ 6(a), above. The 3' NC region had also been described,

e.g., in the publication of Kolykhalov *et al.*, "Identification of a Highly Conserved Sequence Element at the 3' Terminus of Hepatitis C Virus Genome RNA" *J. Virol.* 1996, 70:3363-3371 ("Kolykhalov").[1]

9. My co-inventors and I decided to try the experiments described here to see if HCV-specific primers we had derived from these two regions could be used, along with HIV-specific primers, in a single assay to detect both HIV and HCV. However, before performing these experiments we did not know whether a multiplex PCR assay using the primers from *either* region of the HCV genome would work when combined with HIV-specific primers.

10. The first multiplex PCR assay used the combination of primer sequences set forth in Table I, below. These primers are also recited in the pending claims of this application. Specifically, the first assay used HIV-specific primers that are referred to in the application as JBLTR4 (SEQ ID NO:3),[2] JBLTR6 (SEQ ID NO:4) and JBLTR8 (SEQ ID NO:5). The assay also used HCV-specific primers referred to as C131F25 (SEQ ID NO:1) and C294R25 (SEQ ID NO:2). These HCV-specific primers were designed to specifically amplify the 5' NC region of the HCV genome.

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[1]A copy of the Kolykhalov reference is attached hereto, at Exhibit Tab 2.

[2]The SEQ ID NOS used in this Declaration are those used to identify each primer sequence in the present application.

TABLE I

HIV-specific primers

designation	sequence	seq id no.	comment(s)
JBLTR4	5'-CTGCTTAAGCCTCAATAAAGCTTGCCTTGA-3'	3	forward primer
JBLTR6	5'-GGGTCTGAGGGATCTCTAGTTACCAGAGT-3'	4	reverse primer
JBLTR8	5'-TGTTCGGGCGCCACTGCTAGAGA-3'	5	reverse primer

HCV-specific primers (5' NC region)

designation	sequence	seq id no.	comment(s)
C131F25	5'-GGGAGAGCCATAGTGGTCTGCGGAA-3'	1	forward primer
C294R25	5'-CGGGGCACTCGCAAGCACCCTATCA-3'	2	reverse primer

11. The second multiplex PCR assay used the combination of primer sequences set forth in Table II, below. In particular, the HIV-specific primers from the first multiplex PCR assay (*i.e.*, the primers JBLTR4, JBLTR6 and JBLTR8) were again used. However, the HCV-specific primers used in this second assay were designed to amplify the 3' NC region of the HCV genome. These HCV-specific primers were designated 1F27 and 57R27.

TABLE II

HIV-specific primers

designation	sequence	seq id no.	comment(s)
JBLTR4	5'-CTGCTTAAGCCTCAATAAAGCTTGCCTTGA-3'	3	forward primer
JBLTR6	5'-GGGTCTGAGGGATCTCTAGTTACCAGAGT-3'	4	reverse primer
JBLTR8	5'-TGTTCGGGCGCCACTGCTAGAGA-3'	5	reverse primer

HCV-specific primers (3' NC region)

designation	sequence	seq id no.	comment(s)
1F27	5'-GGTGGCTCCATCTTAGCCCTAGTCACG-3'	N/A	forward primer
57R27	5'-AGGCCAGTATCAGCACTCTCTGCAGTC-3'	N/A	reverse primer

12. Identical clinical samples were tested in each multiplex PCR assay according to the methods set forth in pages 17-19 of the patent application. Briefly, viral loads were quantified in plasma samples from both HIV-positive and HCV-positive patients, using separate commercial assays . Diluted aliquots from these samples were then combined to obtain plasma samples containing zero, five or 25 copies of both HCV and HIV viral RNA. The aliquots were then tested using both multiplex PCR assays.

13. Multiplex PCR assays using the 5' NC primer set successfully and accurately detected both HIV and HCV viral RNA. The results are summarized in the instant patent application at Table 2 (see, page 20 of that application as filed). All samples (100%) containing 25 copies of viral RNA tested positive for both HIV and HCV. Four out of eight (50%) samples containing 5 copies of viral

RNA tested positive for HIV and seven out the eight (88%) tested positive for HCV. These results demonstrate that a viable clinical assay, capable of specifically amplifying both HIV and HCV RNA, can be made by combining the HIV and 5' NC HCV-specific primers shown in Table I.

14. In contrast, an intense side product band was detected in all samples amplified with the 3' NC primer set and a viable assay could not be made using that combination of primers. At 25 copies of viral RNA per reaction, only two out of eight samples correctly tested positive for HCV, and seven out of those eight samples tested positive for HIV.

15. I declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment or both under Section 1001 of Title 18 of the United States Code

and that such willful false statements may jeopardize the validity of the instant application or of any patent issued thereupon.

Respectfully submitted,

Dated: Feb 8, 2002

Kevin M. Gorman, ~~Ph.D.~~ M.D. 2/8/02

Exhibits:

Tab 1: *Curriculum Vitae* for Kevin M. GORMAN, ~~Ph.D.~~ M.D. 2/8/02

Tab 2: Kolykhalov *et al.*, "Identification of a Highly Conserved Sequence Element at the 3' Terminus of Hepatitis C Virus Genome RNA" *J. Virol.* 1996, 70:3363-3371.

EDUCATION

Rochester Institute of Technology (1997 to 1999)
Continuing Education Courses Taken
- Statistical Process Control
- Quality by Experimental Design
- Use of Minitab Statistical Software Package

University of Rochester (1985 to 1990)
Graduate Courses Taken
- Immunology
- Industrial Microbiology
- Microbial Genetics

SUNY College at Plattsburgh (1978-1982)
BS Degree
- Dual Major: Cell Biology and Microbiology
- Minor: Chemistry
- Selected to participate in a special 1-semester internship at the W. Alton Jones Cell Science Center in Lake Placid, NY. Learned theory and developed laboratory skills in cell, tissue and organ culture.

ADDITIONAL SKILLS AND ACTIVITIES

- Skilled in both PC and Macintosh use. Regularly use MS Word, Excel, Excel Graphing, PowerPoint, Visio and Cricket Graph.
- Experienced with using BIAcore (surface plasmon resonance) instrument as a tool to analyze receptor-ligand, antibody-antigen interactions.
- Familiar with using protein purification equipment and instruments.

- Director of a nation-wide endangered species breeding program from 1990 to 1995. Program sponsored by the American Federation of Aviculture. Program goal: to increase the size of the captive population of a South American finch for potential reintroduction into the wild. Responsibilities included coordinating all aspects of breeding and research, training breeders across the US, working with Wildlife Biologists, Veterinarians and with US Fish and Wildlife officials. Additional activities included writing trade journal articles and guest lecturing across the US, and in Frankfurt, Germany.
- Received Eagle Scout and bronze palm award, Boy Scouts of America.